PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/GB2004/002981	International filing date *(day/month/year)* 09.07.2004
Priority date *(day/month/year)* 09.07.2003	
International Patent Classification (IPC) or both national classification and IPC C12N5/06, A61K48/00	
Applicant RAY, Steven	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/002981

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-32 with regard to IA

because:

☒ the said international application, or the said claims Nos. 1-32 with regard to IA relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,7,9-11,13-45
	No:	Claims	1,3,4,6,8,12,46
Inventive step (IS)	Yes:	Claims	7,37-45
	No:	Claims	2,9-11,13-36
Industrial applicability (IA)	Yes:	Claims	33-46
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/002981

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-32 relate inter alia to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The following (groups) of inventions have been identified:

1. method for the differentiation of a stem cell to an adult specialised cell by providing RNA extractable from cells comprising the desired cell type (Claims 1-5, 9, 10, 12-18, 46 (all partially), 6, 11, 19-36, 42-45 (all complete))

2. method for the differentiation of an adult specialised cell to a stem cell by providing RNA extractable from cells comprising the desired cell type (Claims 1-5, 9, 10, 12-18, 46 (all partially), 7, 37-41 (all complete))

3. method for the differentiation of a specialised adult cell to an adult cell of a different speciality by providing RNA extractable from cells comprising the desired cell type (Claims 1-5, 9, 12-18, 46 (all partially), 8 (complete))

The only feature linking the identified (groups of) inventions is the alteration of a property of a cell towards a property of a desired cell type comprising providing RNA extractable from cells comprising said cell type. This feature is neither novel nor inventive because it has been described in the prior art (see for example Niu et al., 1961 or DeCarvalho, 1978).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial appli cability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: NIU M. C. ET AL.: "Ribonucleic acid-induced changes in mammalian cells"

PNAS, vol. 47, 1961, pages 1689-1700, XP002296833

D2: DECARVALHO S.: "Effect of RNA from normal human bone marrow on leukaemic marrow in vivo" NATURE, no. 4872, 16 March 1963 (1963-03-16), pages 1077-1079, XP009036534

D3: DECARVALHO S: "In vitro angiogenic activity of RNA from leukemic lymphocytes." ANGIOLOGY. JUL 1978, vol. 29, no. 7, July 1978 (1978-07), pages 497-505, XP009036537 ISSN: 0003-3197

D4: DE LUCCA F L ET AL: "Effect of the calcium phosphate-mediated RNA uptake on the transfer of cellular immunity of a synthetic peptide of HIV-1 to human lymphocytes by exogenous RNA." MOLECULAR AND CELLULAR BIOCHEMISTRY. DEC 2001, vol. 228, no. 1-2, December 2001 (2001-12), pages 9-14, XP009036575 ISSN: 0300-8177

D5: RASCATI R J ET AL: "Characterization of Fv-1 gene-product-mediated resistance transfer." INTERVIROLOGY. 1981, vol. 15, no. 2, 1981, pages 87-96, XP009036576 ISSN: 0300-5526

D6: DECARVALHO S. AND RAND H. J.: "Comparative effects of liver and tumour ribonucleic acids on the normal liver and the Novikoff hepatoma cells of the rat" NATURE, no. 4767, 11 March 1961 (1961-03-11), pages 815-817, XP009036535

D7: YANG S F ET AL: "Albumin synthesis in mouse uterus in response to liver mRNA." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. MAY 1977, vol. 74, no. 5, May 1977 (1977-05), pages 1894-1898, XP002296835 ISSN: 0027-8424

D8: SANYAL S ET AL: "Effects of RNA on the developmental potentiality of the posterior primitive streak of the chick blastoderm." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. APR 1966, vol. 55, no. 4, April 1966 (1966-04), pages 743-750, XP002296834 ISSN: 0027-8424

D9: WO 02/24873 A (FRANKS CHRISTOPHER RALPH ; DELLA BITTA RUGGERO (IT)) 28 March 2002 (2002-03-28)

1. Novelty

1.1. Claims 1, 3, 4, 8 and 12 lack novelty over either one of D1-D8 which all describe the modification of cell properties by administration of RNA extracted from a desired cell type.

1.2. Claims 6, 19 and 20 lack novelty over D8 which describes the induction of

differentiation in stem cells by RNA extracted from other cells.

1.3. Claim 46 lacks novelty over D5 which describes a screening process for RNA that are able to induce a change of a cellular property, in particular resistance to ectopic retroviruses.

2. Inventive step (Art. 33(3) PCT)

2.1. The prior art contains no indication of a method which would allow to "redifferentiate" a differentiated cell into a stem cell by administration of RNA from the desired cell type (i.e. from stem cells). Claims 7 and 37-45 are thus considered novel and inventive (Art. 33(2) and 33(3) PCT).

2.2. Claim 2 lacks inventive step over D6 which considers the use of RNA extracted from animal organs in the treatment of human disease (p. 816-817, bridging paragraph).

2.3. Claim 33 lacks inventive step over D8 in combination with D9 because it was obvious for the skilled person that the induction of differentiation of stem cells by the administration of RNA would be applicable in the field of stem cell therapy.

2.4. The remaining claims which are dependent on independent claims 1, 19, 20 or 33 as far as they are novel appear not to involve features which could form the basis for an inventive step because they involve mere obvious technical variations of the subject matter of the corresponding independent claims.

3. Industrial application (Art. 33(4) PCT)

For the assessment of the present claims 1-32 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

The subject matter of claim 5 appears to lack sufficiency of disclosure because the application contains no teaching how a genetic transformation of the cells altered by the method of the invention can be achieved. The examples provided appear not to

comprise a test of the genetic manifestation of the transferred phenotype.